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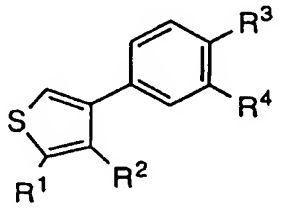
(54) Title: 2-SUBSTITUTED-3,4-DIARYLTHIOPHENE DERIVATIVES AS INHIBITORS OF CYCLOOXYGENASE

(57) Abstract

Disclosed are compounds of formula (I) useful in the treatment of cyclooxygenase mediated diseases such as pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries and Alzheimer's disease. R^3 is selected from the group consisting of (1) $-S(O)_2CH_3$, (2) $-S(O)(NH)CH_3$, (3) $-S(O)NH_2$, and (4) $-S(O)_2NH_2$.



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TITLE OF THE INVENTION

2-SUBSTITUTED-3,4-DIARYLTHIOPHENE DERIVATIVES AS INHIBITORS OF CYCLOOXYGENASE

BACKGROUND OF THE INVENTION

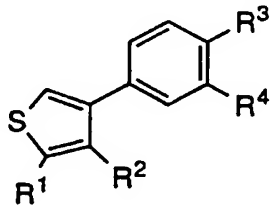
This invention relates to compounds and pharmaceutical compositions for the treatment of cyclooxygenase mediated diseases and methods of treatment thereof.

Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Up until recently, only one form of cyclooxygenase had been characterized, this corresponding to cyclooxygenase-1 or the constitutive enzyme, as originally identified in bovine seminal vesicles. Recently the gene for an inducible form of cyclooxygenase (cyclooxygenase-2) has been cloned, sequenced and characterized from chicken, murine and human sources. This enzyme is distinct from the cyclooxygenase-1 which has now also been cloned, sequenced and characterized from sheep, murine and human sources. The second form of cyclooxygenase, cyclooxygenase-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have physiological and pathological roles, we have concluded that the constitutive enzyme, cyclooxygenase-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, cyclooxygenase-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of cyclooxygenase-2 will have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug (NSAID), and in

addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

SUMMARY OF THE INVENTION

The invention encompasses compounds of Formula I



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which are useful in the treatment of cyclooxygenase mediated diseases, in particular cyclooxygenase-2 mediated diseases.

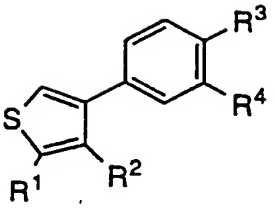
The invention also encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described herein.

The invention also encompasses methods of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases comprising:

administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses compounds of Formula I



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and pharmaceutically acceptable salts thereof wherein:

R1 is selected from the group consisting of

(a) hydrogen,
(b) halo, including fluoro, chloro, bromo and iodo,
(c) CN,
(d) NO_2,
(e) CF_3, and
(f) C_{1-6}alkyl;

R2 is selected from the group consisting of

(a) C_{3-6}alkyl,
(b) mono or di substituted phenyl wherein the substitutents are selected from the group consisting of
  (1) hydrogen,
  (2) halo as defined above,
  (3) C_{1-6}alkoxy,
  (4) C_{1-6}alkylthio,
  (5) CN,
  (6) CF_3,
  (7) C_{1-6}alkyl, and
  (8) N_3,
(c) mono or di substituted heteroaryl wherein heteroaryl is
  (1) a monocyclic aromatic ring of 5 atoms, containing one hetero atom which is S, O or N and optionally 1, 2, or 3 additional hetero atoms which are N, or
  (2) a monocyclic aromatic ring of 6 atoms, containing 1, 2, 3, or 4 hetero atoms which are N, and

wherein the substitutents on the heteroaryl are selected from the group consisting of

(1) hydrogen,
(2) halo as defined above,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,

R^3 is selected from the group consisting of

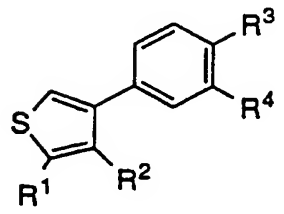
(1) $-S(O)_2CH_3$,
(2) $-S(O)(NH)CH_3$,
(3) $-S(O)NH_2$, and
(4) $-S(O)_2NH_2$;

R^4 is selected from the group consisting of

(1) hydrogen,
(2) halo as defined above,
(3) carboxy, and
(4) CF_3.

For purposes of this specification alkyl is defined to include linear, branched, and cyclic structures, with C_{1-6}alkyl including including methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, C_{1-6}alkoxy is intended to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Likewise, C_{1-6}alkylthio is intended to include alkylthio groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$.

In one genus the invention encompasses compounds of Formula I



I

and pharmaceutically acceptable salts thereof wherein:
R^4 is hydrogen, and
R^2 is selected from the group consisting of

(a) C_{3-6}alkyl,
(b) mono or di substituted phenyl, and
(c) mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of
(1) furanyl,
(2) diazinyl, triazinyl, tetrazinyl,
(3) imidazolyl,
(4) isoxazolyl,
(5) isothiazolyl,
(6) oxadiazolyl,
(7) oxazolyl,
(8) pyrazolyl,
(9) pyrrolyl,
(10) thiadiazolyl,
(11) thiazolyl,
(12) thienyl,
(13) triazolyl,
(14) pyridyl, and
(15) tetrazolyl.

Exemplifying the invention are the compounds of Table 1 including:
3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)thiophene,

2-Nitro-3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl)thiophene,
2-Bromo-3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl)thiophene, and
3-(4-Fluorophenyl)-4-(4-sulfamoylphenyl)thiophene.

In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above.

Within this embodiment the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase-2 and for treating cyclooxygenase-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above.

In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases as disclosed herein comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

Within this embodiment the invention encompasses a method of inhibiting cyclooxygenase-2 and treating cyclooxygenase-2 mediated diseases as disclosed herein comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including

inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

As disclosed elsewhere in this specification in further detail, these diseases include pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries.

Compounds of Formula I are useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns,

injuries, following surgical and dental procedures. In addition, such compounds may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. Compounds of Formula I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma and Alzheimers disease.

By virtue of their high cyclooxygenase-2 (COX-2) activity and/or their specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), compounds of Formula I will prove useful as alternatives to conventional non-steroidal anti-inflammatory drugs (NSAID'S) particularly where such non-steroidal anti-inflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Similarly, compounds of Formula I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; a sedating or non-

sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising administration to a patient in need of such treatment a non-toxic therapeutically effective amount of compound of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

Compounds of the present invention are inhibitors of cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. This activity is illustrated by their ability to selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Accordingly, in one assay, the ability of the compounds of this invention to treat cyclooxygenase mediated diseases can be demonstrated by measuring the amount of prostaglandin E_2 (PGE_2) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a compound of Formula I. The IC50 values represent the concentration of inhibitor required to return PGE_2 synthesis to 50% of that obtained as compared to the uninhibited control. Illustrating this aspect, we have found that Compounds 1 through 25 are more than 100 times more effective in inhibiting COX-2 than they are at inhibiting COX-1. In addition they all have a COX-2 IC50 of 1 nM to 1 μM. By way of comparison, Ibuprofen has an IC50 for COX-2 of 1 μM, and Indomethacin has an IC50 for COX-2 of approximately 100 nM.

For the treatment of any of these cyclooxygenase mediated diseases compounds of Formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of Formula (I) are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 gms per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 gms per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 gm of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

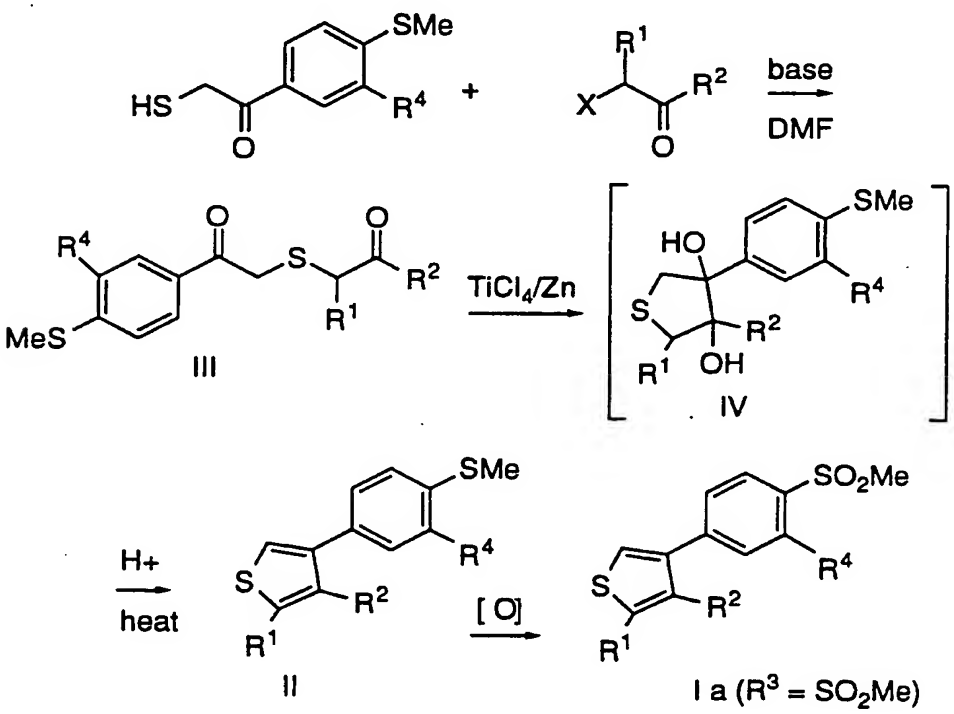
The compounds of the present invention are conviently prepared using the procedures described below.

Method A

The compounds of the present invention can be prepared by the general method described by J. Nakayama *et al.*, *Tetrahedron Lett.*,

26 (16), 1983-1984 (1985). Accordingly, intermediate **III**, obtained from the base catalyzed coupling of an α-mercaptoacetophenone and an α-haloacetophenone, is treated with titanium tetrachloride and zinc at low temperature in an inert solvent such as tetrahydrofuan to give an intermediate 3,4-dihydroxythiolane **IV**. This compound can then be dehydrated by heating it in a solvent such as toluene in the presence of an acid such as p-toluenesulfonic acid to yield **II**. This compound can be oxidized with a reagent such as the magnesium salt of mono-peroxyphtalic acid (MMPP) or m-chloroperoxybenzoic acid (mCPBA) to yield **I**.

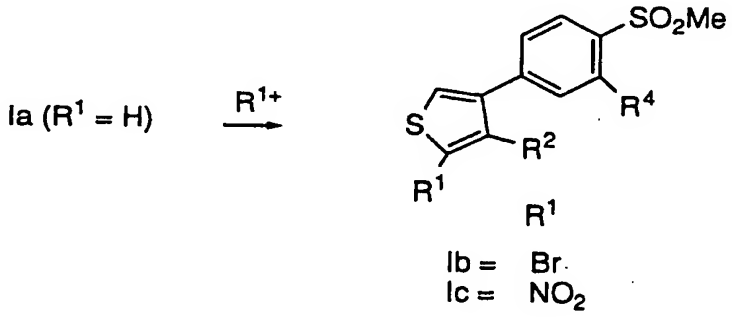
METHOD A



Method B

If **I** contains a substituent R1 which can be introduced by an aromatic electrophilic substitution, this can be carried out either on **I** or **II**. Accordingly, **I** can be treated with a halogenating agent such as bromine in a solvent such as glacial acetic acid to give the desired 2-bromothiophene (R1 = Br). When it is desired to have a nitrogen substituent at this position, for example R1 = NO_2, a cold mixture of **I** in a solvent such as acetic anhydride is treated with nitric acid to introduce the nitro group at the desired position.

METHOD B

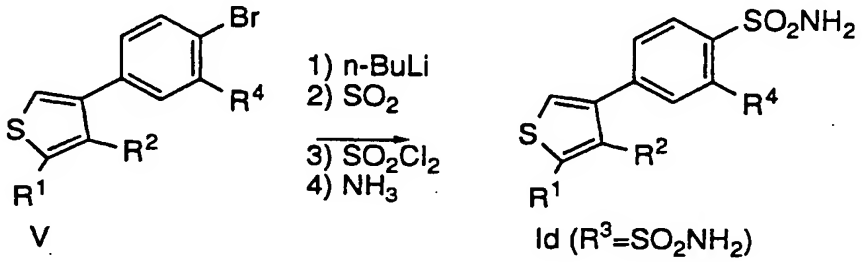


Ib = Br
Ic = NO_2

Method C

When R^3 is a sulfonamide group such as $R^3 = SO_2NH_2$, this substituent can be introduced by treating V with a base such as n-BuLi at low temperature and quenching the anion with sulfur dioxide to give a lithium arylsulfinate intermediate. This intermediate can then be converted to an arylsulfonyl chloride which will react with NH_3 to provide **Id**. This general procedure has been described by T. Hameda and O. Yonemitsu, Synthesis, 852 (1986).

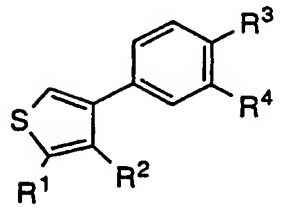
METHOD C



V Id (R^3=SO_2NH_2)

Table I illustrates compounds of Formula I, which are representative of the present invention. Representative biological data and the assays utilized to generate the data is provided immediately thereafter.

TABLE I



Compound	R1	R2	R3	R4
1	H	4-fluorophenyl	-S(O)2CH3	H
2	NO2	"	-S(O)2CH3	H
3	Br	"	-S(O)2CH3	H
4	H	"	-S(O)2NH2	H
5	F	"	-S(O)2CH3	H
6	Cl	"	-S(O)2CH3	H
7	I	"	-S(O)2CH3	H
8	CH3	cyclohexyl	-S(O)2CH3	H
9	CF3	4-fluorophenyl	-S(O)2CH3	H
10	CN	"	-S(O)2CH3	H
11	H	"	-S(O)(NH)CH3	H
12	H	2-pyridyl	-S(O)2CH3	H
13	H	2-thienyl	-S(O)2CH3	H
14	H	-n-pentyl	-S(O)2CH3	H
15	H	4-cyanophenyl	-S(O)2CH3	H
16	H	4-fluorophenyl	-S(O)2CH3	Br
17	H	4-fluorophenyl	-S(O)2CH3	CO2H

Whole Cell Cyclooxygenase Assays

Human osteosarcoma 143.98.2 cells were cultured in DULBECCOS MODIFIED EAGLES MEDIUM (SIGMA) containing 3.7 g/l $NaHCO_3$ (SIGMA), 100 µg/l gentamicin (GIBCO), 25 mM HEPES, pH 7.4 (SIGMA), 100 IU/ml penicillin (FLOW LABS), 100 µg/ml streptomycin (FLOW LABS), 2 mM glutamine (FLOW LABS) and 10% fetal bovine serum (GIBCO). Cells were maintained at 37°C, 6% CO_2 in 150 cm^2 tissue culture flasks (CORNING). For routine subculturing, media was removed from confluent cultures of cells, which were then incubated with 0.25% trypsin/0.1% EDTA (JRH BIOSCIENCES) and incubated at room temperature for approximately 5 minutes. The trypsin solution was then aspirated, and cells resuspended in fresh medium and dispensed at a ratio of 1:10 or 1:20 into new flasks.

U-937 cells (ATCC CRL 1593) were cultured in 89% RPMI-1640 (SIGMA), 10% fetal bovine serum (GIBCO), containing 50 IU/ml penicillin (FLOW LABS), 50 µg/ml streptomycin (FLOW LABS) and 2 g/l $NaHCO_3$ (SIGMA). Cells were maintained at a density of 0.1-2.0 x 10^6/ml in 1 liter spinner flasks (CORNING) at 37°C, 6% CO_2. For routine subculturing, cells were diluted in fresh medium and transferred to fresh flasks.

Assay Protocol

For cyclooxygenase assays, osteosarcoma 143.98.2 cells were cultured in 1 ml of media in 24-well multidishes (NUNCLON) until confluent. The number of cells per assay was determined from replicate plates prior to assays, using standard procedures. Immediately prior to cyclooxygenase assays, media was aspirated from cells, and the cells washed once with 2 ml of Hanks balanced salts solution (HBSS; SIGMA) prewarmed to 37°C. 1 ml of prewarmed HBSS was then added per well.

Immediatley prior to cyclooxygenase assays, the appropriate number of U-937 cells were removed from spinner cultures and centrifuged at 300 x g for 10 minutes. The supernatant was

decanted and cells washed in 50 ml of HBSS prewarmed to 37°C. Cells were again pelleted at 300 x g for 10 minutes and resuspended in prewarmed HBSS to a final cell density of approximately 1.5 x 10^6 cells/ml. 1 ml aliquots of cell suspension were transferred to 1.5 ml microcentrifuge tubes or 24-well multidishes (NUNCLON).

Following washing and resuspension of osteosarcoma 143 and U-937 cells in 1 ml of HBSS, 1 µl of test compounds or DMSO vehicle were added, and samples gently mixed. All assays were performed in triplicate. Samples were then incubated for 15 minutes at 37°C, prior to the addition of 10 µl of peroxide-free arachidonic acid (CAYMAN) diluted to 1 mM in HBSS. Control samples contained ethanol vehicle instead of arachidonic acid. Samples were again gently mixed and incubated for a further 10 minutes at 37°C. For osteosarcoma cells, reactions were then stopped by the addition of 100 µl of 1N HCl, with mixing, or by the rapid removal of media directly from cell monolayers. For U-937 cells, reactions in multiwell dishes or microcentrifuge tubes were stopped by the addition of 100 µl of 1N HCl, with mixing. Samples assayed in 24-multidishes were then transferred to microcentrifuge tubes. If necessary, samples were stored at 4°C prior to analysis of PGE_2 levels.

Quantitation of PGE_2 Concentrations

Osteosarcoma 143.98.2 and U-937 samples were neutralized by the addition of 100 µl of 1N NaOH. Samples were then mixed by vortexing, and PGE_2 levels measured using a PGE_2 radio-immunoassay (NEW ENGLAND NUCLEAR-DUPONT) according to the manufacturers instructions. This procedure was automated using a BIOMEK 1000 (BECKMAN). Levels of PGE_2 were calculated from the standard curve determined using BECKMAN IMMUNOFIT EIA/RIA analysis software.

Results

TABLE 2

Compound #	Drug Concentration nM	% Of Inhibition			
		Whole Cells		Microsomes	
		COX 2 (osteosarcoma)	COX 1 (U937)	COX 2 (osteosarcoma)	COX 1 (U937)
1	10	38	1		
	100	87	-2	98	15
2	10	27	0	20	5
	100	95	0	45	1
3	10	62	0	36	3
	100	84	0	81	-5
4	10	69	8	54	-5
	100	94	21	63	-8

EXAMPLES

The invention will now be illustrated by the following non-limiting examples. Unless stated otherwise: (i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C; (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 me. Hg) with a bath temperature of up to 60°C; (iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; (iv) melting points are uncorrected and `d' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in soee preparations; (v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; (vi) yields are given for

illustration only; (vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal; (viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)). Further, unless otherwise stated the following abbreviations have the indicated meanings:

DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
Et3N	=	triethylamine
MMMP	=	magnesium monoperoxyphthalate
Ph	=	phenyl
r.t.	=	room temperature
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography

Alkyl group abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl

Optical Isomers - Diastereomers - Geometric Isomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

EXAMPLE 1 (Compound 1)

3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)thiophene

Step 1: 4'-(Methylthio)-2-chloroacetophenone

To a -5°C solution of thioanisole (26.4 g) and chloroacetyl chloride (27 g) in dichloromethane (600 mL) was added $AlCl_3$ (33.2 g) portion-wise. The mixture was allowed to warm up to 25°C and was stirred for 16 h. It was poured over ice water and stirred for 1.5 h. The mixture was extracted with CH_2Cl_2 (2 x 600 mL) and the combined extracts were washed with brine and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue swished in 1:25 ethyl acetate:hexanes. The solid was filtered and dried to yield 18 g of the title compound.

^1H NMR (CD_3COCD_3): δ 2.55 (3H, s), 4.95 (2H, s), 7.35-8.0 (4H, m).

Step 2: 4'-(Methylthio)-2-(acetylthio)acetophenone

To a 0°C suspension of 4'-(methylthio)-2-chloro-acetophenone (18 g) from Step 1 in THF (20 mL) and DMF (180 mL) was added potassium thioacetate (11.6 g). The mixture was warmed to 25°C and stirred 1.5 h. It was poured over ice/dilute $NaHCO_3$. The mixture was extracted with ethyl acetate:ether (2 x 200 mL) and the combined extracts were washed with H_2O, brine and dried with $MgSO_4$. After removal of the solvents *in vacuo*, the residue was

swished in 1:25 ethyl acetate:hexanes and the solid was filtered and dried to yield 18 g of the title compound.
^{1}H NMR (CD_3COCD_3): δ 2.35 (3H, s), 2.55 (3H, s), 4.45 (2H, s), 7.35-7.95 (4H, m).

Step 3: 4'-(Methylthio)phenacyl-4-fluorophenacyl sulfide

To a -5°C solution of 4'-(methylthio)-2-(acetylthio)-acetophenone (18 g) from Step 2 in THF (50 mL) and DMF (100 mL) was added hydrazine (2.6 mL). After 0.5 h Cs_2CO_3 (26 g) and 4-fluorophenacylchloride (21.6 g) were added and the mixture was poured over ice/dilute HCl. It was extracted with ethyl acetate (2 x 200 mL) and the combined extracts were washed with H_2O, brine and dried with $MgSO_4$. After removal of the solvents the residue was purified by chromatography to yield the title compound (12.76 g).
^{1}H NMR (CD_3COCD_3): δ 2.55 (3H, s), 4.05 (2H, s), 4.1 (2H, s), 7.2-8.2 (8H, m).

Step 4: 3-(4-Fluorophenyl)-4-((4-methylthio)phenyl)thiophene

To a -35°C solution of 4'-(methylthio)phenacyl-4-fluorophenacyl sulfide (8.8 g) from Step 3 in THF (225 mL) was added $TiCl_4$ (23.71 g) dropwise and the mixture was stirred for 0.5 h. Zinc powder (16.4 g) was added portionwise with vigourous stirring and the dark green suspension was stirred for 1 h at -35°C. The mixture was transferred via a canula to ice cold 1 M tartaric acid (1000 mL) and the mixture was stirred for 1 h. It was extracted with ethyl acetate (3 x 200 mL) and the combined extracts were washed with brine and dried with $MgSO_4$. After removal of the solvents the residue was dissolved in toluene (50 mL) containing p-TsOH (50 mg) and the mixture was refluxed for 3 h. The solvent was removed and the residue purified by chromatography to afford the title compound.
^{1}H NMR (CD_3COCD_3): δ 2.45 (3H, s), 7.0-7.5 (10H, m).

Step 5: 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)thiophene

To a 0°C suspension of 3-(4-fluorophenyl)-4-((4-methylthio)phenyl)thiophene (3 g) from Step 4 in MeOH and CH_2Cl_2 (50 mL) was added portionwise MMPP (6.8 g) and the mixture was allowed to react for 3 h while warming to 25°C. It was diluted with CH_2Cl_2 (50 mL) and filtered through celite. The filtrate was concentrated to dryness and purified by chromatography to yield the title compound (3.16 g).

^1H NMR (CD_3COCD_3): δ 3.05 (3H, s), 6.95-7.9 (10H, m).

EXAMPLE 2 (Compound 2)

2-Nitro-3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl)thiophene

To a 0°C suspension of 3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl) thiophene (1.32 g) from Example 1 in nitromethane (10 mL) and acetic anhydride (10 mL) was added 70% aqueous HNO_3 (320 µL). The cold bath was removed and the mixture was stirred 2 h at 25°C. It was then poured over ice H_2O and extracted with ethyl acetate (3 x 25 mL). The combined extracts were washed with brine, dried with $MgSO_4$ and the solvents were removed *in vacuo*. The residue was purified by chromatography to afford the title compound (858 mg).

Analysis calculated for $C_{17}H_{12}FNO_4S_2$:
C, 54.10; H, 3.21; N, 3.71.
Found: C, 53.77; H, 3.39; N, 3.62.

EXAMPLE 3 (Compound 3)

2-Bromo-3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl)thiophene

To a 0°C solution of 3-(4-fluorophenyl)-4-((4-methylsulfonyl)phenyl)thiophene (332 mg) from Example 1 in CH_2Cl_2 (2 mL) and acetic acid (2 mL) was added a 1 M solution of Br_2 in CCl_4 (1.1 mL) and the mixture was reacted for 2 h at 0°C. The mixture was then concentrated to dryness and the residue purified by chromatography to afford the title compound (203 mg).

Analysis calculated for $C_{17}H_{12}BrFS_2O_2$:
C, 49.65; H, 2.94.
Found: C, 49.83; H, 2.89.

EXAMPLE 4 (Compound 4)

3-(4-Fluorophenyl)-4-(4-sulfamoylphenyl)thiophene

Step 1: 3-(4-Fluorophenyl)-4-(4-bromophenyl)thiophene

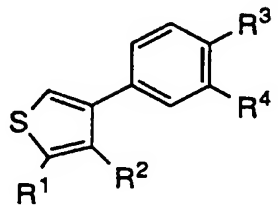
Following the procedures of Example 1, Steps 2-7, but replacing 4'-(methylthio)-2-chloroacetophenone by 4-bromophenyl bromide in Step 2, there was obtained the title compound.
^1H NMR (CD_3COCD_3): δ 7.0-7.3 (4H, m), 7.4-7.6 (6H, m)

Step 2: 3-(4-Fluorophenyl)-4-(4-sulfamoylphenyl)thiophene

To a -78°C solution of 3-(4-fluorophenyl)-4-(4-bromophenyl)thiophene (999 mg) in tetrahydrofuran (10 mL) was added 2.27 M n-BuLi (1.45 mL) and the mixture was stirred for 0.5 h at -78°C. It was then transferred dropwise into a -78°C solution of sulfur dioxide (10 mL) and tetrahydrofuran (10 mL) and the mixture was allowed to warm slowly to 25°C. The solvents were removed *in vacuo* and the solid obtained was suspended in hexanes (15 mL) and the suspension was cooled to 0°C. A 1 M dichloromethane solution of sulfuryl chloride (3 mL) was then added dropwise and the mixture was stirred for 0.5 h at 25°C. It was cooled again at 0°C and filtered. The solid obtained was taken into tetrahydrofuran and the mixture was cooled to 0°C before NH_3 was bubbled in for a few minutes. Removal of the solvents followed by purification on silica gel yielded the title compound (350 mg).
^1H NMR (CD_3COCD_3): δ 6.5-6.6 (2H, broad), 7.0-7.4 (6H, m), 7.55 (1H, d), 7.65 (1H, d), 7.75-7.8 (2H, d).

WHAT IS CLAIMED IS:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof wherein:

R1 is selected from the group consisting of

(a) hydrogen,
(b) halo, including fluoro, chloro, bromo and iodo,
(c) CN,
(d) NO_2,
(e) CF_3, and
(f) C_{1-6}alkyl;

R2 is selected from the group consisting of

(a) C_{3-6}alkyl,
(b) mono or di substituted phenyl wherein the substitutents are selected from the group consisting of
  (1) hydrogen,
  (2) halo as defined above,
  (3) C_{1-6}alkoxy,
  (4) C_{1-6}alkylthio,
  (5) CN,
  (6) CF_3,
  (7) C_{1-6}alkyl,
  (8) N_3,
(c) mono or di substituted heteroaryl wherein heteroaryl is

(1) a monocyclic aromatic ring of 5 atoms, containing one hetero atom which is S, O or N and optionally 1, 2, or 3 additional hetero atoms which are N, or
(2) a monocyclic aromatic ring of 6 atoms, containing 1, 2, 3, or 4 hetero atoms which are N, and

wherein the substitutents on the heteroaryl are selected from the group consisting of
(1) hydrogen,
(2) halo as defined above,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3;

R^3 is selected from the group consisting of
(1) $-S(O)_2CH_3$,
(2) $-S(O)(NH)CH_3$,
(3) $-S(O)NH_2$, and
(4) $-S(O)_2NH_2$;

R^4 is selected from the group consisting of
(1) hydrogen,
(2) halo as defined above,
(3) carboxy, and
(4) CF_3.

2. A compound according to Claim 1 wherein R^2 is selected from the group consisting of
(a) C_{3-6}alkyl,
(b) mono or di substituted phenyl, and
(c) mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of
(1) furanyl,
(2) diazinyl, triazinyl, tetrazinyl,

(3) imidazolyl,
(4) isoxazolyl,
(5) isothiazolyl,
(6) oxadiazolyl,
(7) oxazolyl,
(8) pyrazolyl,
(9) pyrrolyl,
(10) thiadiazolyl,
(11) thiazolyl,
(12) thienyl,
(13) triazolyl,
(14) pyridyl, and
(15) tetrazolyl, and

wherein the substitutents on the phenyl or heteroaryl are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl, and
(8) N_3.

3. A compound according to Claim 2 wherein R^2 is selected from the group consisting of

(a) cyclohexyl, and
(b) mono or di substituted phenyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,

(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3;

R^4 is selected from the group consisting of
(1) hydrogen,
(2) halo as defined above, and
(3) carboxy.

4. A compound according to Claim 3 wherein
R^1 is selected from the group consisting of
(a) hydrogen,
(b) halo selected from the group consisting of fluoro, chloro and bromo,
(c) CN,
(d) C_{1-3}alkyl;
R^2 is selected from the group consisting of
(a) cyclohexyl, and
(b) mono or di substituted phenyl wherein the substitutents are selected from the group consisting of
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo,
(3) C_{1-3}alkoxy,
(4) C_{1-3}alkylthio,
(5) CN, and
(6) C_{1-3}alkyl;
R^4 is hydrogen.

5. A compound according to Claim 4 wherein
R^3 is selected from the group consisting of
(1) $-S(O)_2CH_3$,
(2) $-S(O)(NH)CH_3$, and
(3) $-S(O)NH_2$, and

(4) $-S(O)_2NH_2$.

6. A compound according to Claim 5 wherein R^1 is selected from the group consisting of

(a) hydrogen,
(b) halo selected from the group consisting of fluoro, chloro and bromo,
(c) CN, and
(d) C_{1-3}alkyl;

R^2 is selected from the group consisting of

(a) cyclohexyl, and
(b) mono substituted phenyl wherein the substitutents are selected from the group consisting of
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo,
(3) C_{1-3}alkoxy,
(4) C_{1-3}alkylthio,
(5) CN, and
(6) C_{1-3}alkyl.

7. A compound according to Claim 2 wherein R^2 is a mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) furanyl,
(2) diazinyl, triazinyl, tetrazinyl,
(3) imidazolyl,
(4) isoxazolyl,
(5) isothiazolyl,
(6) oxadiazolyl,
(7) oxazolyl,
(8) pyrazolyl,
(9) pyrrolyl,
(10) thiadiazolyl,

(11) thiazolyl,
(12) thienyl,
(13) triazolyl,
(14) pyridyl, and
(15) tetrazolyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,

R^4 is selected from the group consisting of

(1) hydrogen,
(2) halo as defined above,
(3) carboxy.

8. A compound according to Claim 7 wherein R^2 is a mono or di substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) 2-furanyl,
(2) 3-furanyl,
(3) 2-thienyl,
(4) 3-thienyl,
(5) 3-isoxazolyl,
(6) 4-isoxazolyl,
(7) 5-isoxazolyl,
(8) 3-isothiazolyl,
(9) 4-isothiazolyl,
(10) 5-isothiazolyl,
(11) 2-oxazolyl,

(12) 4-oxazolyl,
(13) 5-oxazolyl,
(14) 2-thiazolyl,
(15) 4-thiazolyl,
(16) 5-thiazolyl,
(17) 1,2,3-thiadiazol-4-yl,
(18) 1,2,3-thiadiazol-5-yl,
(19) 1,2,4-thiadiazol-3-yl,
(20) 1,2,4-thiadiazol-5-yl,
(21) 1,3,4-thiadiazol-2-yl,
(22) 1,2,5-thiadiazol-3-yl,
(23) 1,2,3-oxadiazol-4-yl,
(24) 1,2,3-oxadiazol-5-yl,
(25) 1,2,4-oxadiazol-3-yl,
(26) 1,2,4-oxadiazol-5-yl,
(27) 1,3,4-oxadiazol-2-yl,
(28) 1,2,5-oxadiazol-3-yl,
(29) pyrazol-4-yl,
(30) pyrazol-5-yl,
(31) 1,2,3-triadiazol-4-yl,
(32) 1,2,3-triadiazol-5-yl,
(33) 1,2,4-triadiazol-3-yl,
(34) 1,2,4-triadiazol-5-yl,
(35) 1,2-diazinyl,
(36) 1,3-diazinyl,
(37) 1,4-diazinyl,
(38) 1,2,3,4-tetrazin-5-yl,
(39) 1,2,4,5-tetrazin-4-yl,
(40) 1,3,4,5-tetrazin-2-yl,and
(41) 1,2,3,5-tetrazin-4-yl.

9. A compound according to Claim 8 wherein the heteroaryl is selected from the group consisting of

(1) 3-isoxazolyl,

(2) 4-isoxazolyl,
(3) 5-isoxazolyl,
(4) 3-isothiazolyl,
(5) 4-isothiazolyl,
(6) 5-isothiazolyl,
(7) 2-oxazolyl,
(8) 4-oxazolyl,
(9) 5-oxazolyl,
(10) 2-thiazolyl,
(11) 4-thiazolyl,
(12) 5-thiazolyl,
(13) 1,2,3-thiadiazol-4-yl,
(14) 1,2,3-thiadiazol-5-yl,
(15) 1,2,4-thiadiazol-3-yl,
(16) 1,2,4-thiadiazol-5-yl,
(17) 1,3,4-thiadiazol-2-yl,
(18) 1,2,5-thiadiazol-3-yl,
(19) 1,2,3-oxadiazol-4-yl,
(20) 1,2,3-oxadiazol-5-yl,
(21) 1,2,4-oxadiazol-3-yl,
(22) 1,2,4-oxadiazol-5-yl,
(23) 1,3,4-oxadiazol-2-yl,
(24) 1,2,5-oxadiazol-3-yl,
(25) 1,2-diazinyl,
(26) 1,3-diazinyl, and
(27) 1,4-diazinyl.

10. A compound according to Claim 9 wherein the hetreoaryl is selected from the group consisting of
(1) 2-oxazolyl,
(2) 4-oxazolyl,
(3) 5-oxazolyl,
(4) 3-thiazolyl,
(5) 4-thiazolyl,

(6) 5-thiazolyl,
(7) 1,3,4-thiadiazol-2-yl,
(8) 1,2,5-thiadiazol-3-yl,
(9) 1,3,4-oxadiazol-2-yl,
(10) 1,2,5-oxadiazol-3-yl,
(11) 1,2-diazinyl,
(12) 1,3-diazinyl, and
(13) 1,4-diazinyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo,
(3) C_{1-3}alkoxy,
(4) C_{1-3}alkylthio,
(5) CN, and
(6) C_{1-3}alkyl.

11. A compound according to Claim 10 wherein the hetreoaryl is selected from the group consisting of

(1) 2-oxazolyl,
(2) 4-oxazolyl,
(3) 5-oxazolyl,
(4) 2-thiazolyl,
(5) 4-thiazolyl,
(6) 5-thiazolyl,
(7) 1,3,4-thiadiazol-2-yl,
(8) 1,2,5-thiadiazol-3-yl,
(9) 1,3,4-oxadiazol-2-yl,
(10) 1,2,5-oxadiazol-3-yl,
(11) 1,2-diazinyl,
(12) 1,3-diazinyl, and
(13) 1,4-diazinyl.

12. A compound according to Claim 11 wherein
R1 is selected from the group consisting of
(a) hydrogen,
(b) halo selected from the group consisting of fluoro, chloro and bromo,
(c) CN, and
(d) C_{1-3}alkyl;
R4 is hydrogen.

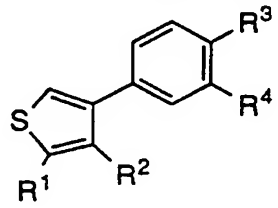
13. A compound according to Claim 11 wherein
R3 is selected from the group consisting of
(1) $-S(O)_2CH_3$, and
(2) $-S(O)_2NH_2$;
R4 is hydrogen.

14. A compound according to Claim 13 wherein
R1 is selected from the group consisting of
(a) hydrogen,
(b) halo selected from the group consisting of fluoro, chloro and bromo,
(c) CN, and
(d) C_{1-3}alkyl;
R2 is selected from the group consisting of
(1) 2-oxazolyl,
(2) 4-oxazolyl,
(3) 5-oxazolyl,
(4) 2-thiazolyl,
(5) 4-thiazolyl,
(6) 5-thiazolyl,
(7) 1,3,4-thiadiazol-2-yl,
(8) 1,2,5-thiadiazol-3-yl,
(9) 1,3,4-oxadiazol-2-yl,
(10) 1,2,5-oxadiazol-3-yl,
(11) 1,2-diazinyl,

(12) 1,3-diazinyl, and
(13) 1,4-diazinyl,
wherein the substitutents are selected from the group consisting of
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo,
(3) C1-3alkoxy,
(4) C1-3alkylthio,
(5) CN, and
(6) C1-3alkyl;

R4 is hydrogen.

15. A compound of Formula I wherein



R1	R2	R3	R4
H	4-fluorophenyl	$-S(O)_2CH_3$	H
NO_2	"	$-S(O)_2CH_3$	H
Br	"	$-S(O)_2CH_3$	H
H	"	$-S(O)_2NH_2$	H
F	"	$-S(O)_2CH_3$	H
Cl	"	$-S(O)_2CH_3$	H
I	"	$-S(O)_2CH_3$	H
CH_3	cyclohexyl	$-S(O)_2CH_3$	H
CF_3	4-fluorophenyl	$-S(O)_2CH_3$	H
CN	"	$-S(O)_2H_3$	H
H	"	$-S(O)(NH)CH_3$	H
H	2-pyridyl	$-S(O)_2CH_3$	H
H	2-thienyl	$-S(O)_2CH_3$	H
H	-n-pentyl	$-S(O)_2CH_3$	H
H	4-cyanophenyl	$-S(O)_2CH_3$	H
H	4-fluorophenyl	$-S(O)_2CH_3$	Br
H	4-fluorophenyl	$-S(O)_2CH_3$	CO_2H

16. A pharmaceutical composition for inhibiting cyclooxygenase comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound or salt according to claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

17. A pharmaceutical composition for inhibiting cycloxygenase-2 comprising a pharmaceutically acceptable carrier and

a non-toxic therapeutically effective amount of compound or salt according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

18. A method of inhibiting cyclooxygenase comprising: administration to a patient in need of such inhibition of a non-toxic therapeutically effective amount of a compound according to Claim 1.

19. A method of inhibiting cyclooxygenase-2 comprising: administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1.

20. A pharmaceutical composition for the treatment of cyclooxygenase-2 mediated disease comprising a non-toxic therapeutically effective amount of compound according to Claim 1 and at least one or more ingredients selected from a pain reliever including acetaminophen or phenacetin; a potentiator including caffine; an H2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudopheorine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desocyephedrine; an antitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine.

21. A cyclooxygenase inhibitor pharmaceutical composition comprising an acceptable cyclooxygenase inhibiting amount of a compound of formula (I), as defined in Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

22. Use of a compound of formula (I) as defined in Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cyclooxygenase mediated diseases.

23. A compound of formula (I), as defined in Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, or a pharmaceutically acceptable salt thereof for use in inhibiting cyclooxygenase.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 94/00264

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D333/18 C07D333/28 C07D333/44 C07D409/04 A61K31/38 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 087 629 (E.I. DU PONT DE NEMOURS & CO.) 7 September 1983 see page 8; claims ---	1,16
A	EP,A,0 365 089 (MERCK & CO., INC.) 25 April 1990 see claims ---	1,16
E	WO,A,94 15932 (G.D. SEARLE & CO.) 21 July 1994 see the whole document -----	1-23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 August 1994	-5. 09. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA94/00264

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18 and 19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/ composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/CA 94/00264

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0087629	07-09-83	AU-B-	553269	10-07-86
		AU-A-	1146083	08-09-83
		CA-A-	1242725	04-10-88
		JP-C-	1654086	13-04-92
		JP-B-	3014312	26-02-91
		JP-A-	58159489	21-09-83
		SU-A-	1250172	07-08-86
		US-A-	4590205	20-05-86
		US-A-	4820827	11-04-89
EP-A-0365089	25-04-90	JP-A-	2275875	09-11-90
WO-A-9415932	21-07-94	NONE		